510(k) Summary

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BD Diagnostics BD MAX™ Cdiff Assay

Submitted by: GeneOhm Sciences Canada Inc. (BD Diagnostics)
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Device:

510(k) Number: K130470

Trade Name: BD MAX™ Cdiff Assay

Common Name: *Clostridium difficile tcdB* detection assay

Type of Test: Qualitative Nucleic Acid Amplification Test for *C. difficile* toxin B gene from liquid or soft stool specimens

Classification: II

Regulation Name: *Clostridium difficile* Toxin Gene Amplification Assay

Regulation Number: 866.3130

Product Code: OZN, OOI

Panel: Microbiology (83)

Predicate Device: BD GeneOhm™ Cdiff Assay

Predicate 510(k) number: K081920

Intended Use:

The BD MAX™ Cdiff Assay performed on the BD MAX™ System is an automated *in vitro* diagnostic test for the direct, qualitative detection of the *Clostridium difficile* toxin B gene (*tcdB*) in human liquid or soft stool specimens from patients suspected of having *C. difficile* infection (CDI). The test, performed directly on the specimen, utilizes real-time polymerase chain reaction (PCR) for the amplification of *C. difficile* toxin B gene DNA and fluorogenic target-specific hybridization probes for the detection of the amplified DNA. The BD MAX™ Cdiff Assay is intended to aid in the diagnosis of CDI.

Indication for Use:

The BD MAX™ Cdiff Assay performed on the BD MAX™ System is an automated *in vitro* diagnostic test for the direct, qualitative detection of the *Clostridium difficile* toxin B gene (*tcdB*) in human liquid or soft stool specimens from patients suspected of having *C. difficile* infection (CDI). The test,

performed directly on the specimen, utilizes real-time polymerase chain reaction (PCR) for the amplification of *C. difficile* toxin B gene DNA and fluorogenic target-specific hybridization probes for the detection of the amplified DNA. The BD MAX™ Cdiff Assay is intended to aid in the diagnosis of CDI.

Special Conditions for Use Statement: For prescription use

Special Instrument Requirements: The BD MAX™ System

Device Description:

The BD MAX™ System and the BD MAX™ Cdiff Assay are comprised of an instrument with associated hardware and accessories, disposable microfluidic cartridges, master mixes, unitized reagent strips, extraction reagents, and sample buffer tubes. The instrument automates sample preparation including target lysis, DNA extraction and concentration, reagent rehydration, and target nucleic acid amplification and detection using real-time PCR. The assay includes a Sample Processing Control (SPC) that is present in the Extraction Tube. The SPC monitors DNA extraction steps, thermal cycling steps, reagent integrity and the presence of inhibitory substances. The BD MAX™ System software automatically interprets test results. A test result may be called as NEG (negative), POS (positive) or UNR (unresolved) based on the amplification status of the target and of the Sample Processing Control. IND (indeterminate) or INC (incomplete) results are due to BD MAX™ System failure.

Test Principle:

The BD MAX™ Cdiff Assay performed on the BD MAX™ System is an automated *in vitro* diagnostic test for the direct, qualitative detection of the *Clostridium difficile* toxin B gene (*tcdB*) in human liquid or soft stool specimens from patients suspected of having *C. difficile* infection (CDI).

A liquid or soft stool specimen is collected and transported to the laboratory. For testing, a disposable 10µL inoculating loop is dipped into the stool material and the contents dispersed into a BD MAX™ Cdiff Sample Buffer Tube. The Sample Buffer Tube is closed with a septum cap and vortexed. A worklist is created and the Sample Buffer Tube, the BD MAX™ Cdiff unitized reagent strip and the BD MAX™ PCR Cartridge are loaded onto the BD MAX™ System.

Following enzymatic cell lysis, the released nucleic acids are captured on magnetic beads. The beads, with the bound nucleic acids, are washed using Wash Buffer and the nucleic acids are eluted by heat in Elution Buffer. Eluted DNA is neutralized using Neutralization Buffer and transferred to a Master Mix to rehydrate PCR reagents. After reconstitution, the BD MAX™ System dispenses a fixed volume of PCR-ready solution containing extracted nucleic acids into the BD MAX™ PCR Cartridge. Microvalves in the BD MAX™ PCR Cartridge are sealed by the system prior to initiating PCR to contain the amplification mixture, thus preventing evaporation and contamination.

The amplified DNA targets are detected using hydrolysis (TaqMan®) probes, labeled at one end with a fluorescent reporter dye (fluorophore), and at the other end, with a quencher moiety. Probes labeled with different fluorophores are used to detect *tcdB* and SPC amplicons in two different

optical channels of the BD MAX™ System. When the probes are in their native state, the fluorescence of the fluorophore is quenched due to its proximity to the quencher. However, in the presence of target DNA, the probes hybridize to their complementary sequences and are hydrolyzed by the 5'-3' exonuclease activity of the DNA polymerase as it synthesizes the nascent strand along the DNA template. As a result, the fluorophores are separated from the quencher molecules and fluorescence is emitted. The amount of fluorescence detected in the two optical channels used for the BD MAX™ Cdiff Assay is directly proportional to the quantity of the corresponding probe that is hydrolyzed. The BD MAX™ System monitors these signals at each cycle of the PCR and interprets the data at the end of the program to provide a final result.

Substantial Equivalence:

Table 1 shows the similarities and differences between the BD MAX™ Cdiff Assay and the predicate device.

Table 1: Substantial Equivalence Information

Item	Device	Predicate
	BD MAX™ Cdiff Assay	**BD GeneOhm™ Cdiff Assay (K081920)**
	SIMILARITIES	
Intended Use	The BD MAX™ Cdiff Assay performed on the BD MAX™ System is an automated *in vitro* diagnostic test for the direct, qualitative detection of the *Clostridium difficile* toxin B gene (*tcdB*) in human liquid or soft stool specimens from patients suspected of having *C. difficile* infection (CDI). The test, performed directly on the specimen, utilizes real-time polymerase chain reaction (PCR) for the amplification of *C. difficile* toxin B gene DNA and fluorogenic target-specific hybridization probes for the detection of the amplified DNA. The BD MAX™ Cdiff Assay is intended to aid in the diagnosis of CDI.	The BD GeneOhm™ Cdiff Assay is a rapid *in vitro* diagnostic test for the direct, qualitative detection of *C. difficile* toxin B gene (*tcdB*) in human liquid or soft stool specimens from patients suspected of having *Clostridium difficile*-associated disease (CDAD). The test, based on real-time PCR, is intended for use as an aid in diagnosis of CDAD. The test is performed directly on the specimen, utilizing polymerase chain reaction (PCR) for the amplification of specific targets and fluorogenic target-specific hybridization probes for the detection of the amplified DNA.
Mode of detection for toxin B	Presence of the *toxin B (tcdB)* gene	Presence of the *toxin B (tcdB)* gene
Specimen Type	Liquid and soft stool specimens	Liquid and soft stool specimens
Assay Format	Amplification: PCR Detection: Fluorogenic target-specific hybridization	Amplification: PCR Detection: Fluorogenic target-specific hybridization
Interpretation of test results	Automated (Diagnostic software of BD MAX™ system)	Automated (Diagnostic software of SmartCycler® system)
	DIFFERENCES	
Analysis Platform	BD MAX™ System	SmartCycler® System
PCR Sample Preparation	Automated by the BD MAX™ System	Manual
Detection Probes	TaqMan® Probe	Molecular Beacon Probe

Assay Controls	**Specimen Processing Control (SPC)**	**Positive (DNA from *Clostridium difficile* bearing the *tcdB* gene ATCC 43255)** **Negative (DNA from *Escherichia coli* ATCC 25922)** **Internal procedural control**

Analytical Performance:

Precision

Within-laboratory precision was evaluated for the BD MAX™ Cdiff Assay at one (1) site. The Precision panel consisted of 5 sample categories in simulated sample matrix as follows:

- Moderate Positive (MP): 2 – 5 x LoD
- Low Positive (LP): 1- 2 x LoD
- High Negative 1:10 (HN1:10): 10-fold dilution of 1 x LoD
- High Negative 1:100 (HN1:100): 100-fold dilution of 1 x LoD
- True Negative (Neg)

Testing was performed in duplicate, over 12 days, with 2 runs per day, by 2 technologists. Precision study results for Neg, LP and MP samples demonstrated 100% agreement. Precision study results for HN1:100 and HN1:10 demonstrated agreement of 95.8% and 58.3%, respectively. Precision performance was acceptable for the LP, MP, and Neg sample categories. No specific acceptance criteria were defined for either of the high negative sample categories.

Reproducibility

Reproducibility was evaluated with a panel that consisted of the same sample categories described for the Precision study. Samples in each category were tested in triplicate, on 5 distinct days, wherein each day 2 panels were tested by 2 technologists, at 3 clinical sites using 1 lot of reagents (Site-to-Site). One of these clinical sites participated in an extended study where 2 additional lots of reagents were tested (Lot-to-Lot). Results are shown for each sample category.

For Site-to-Site Reproducibility, the overall percent agreement was 100% for MP, LP and Neg categories. The Site-to-Site Reproducibility results demonstrated 92.2% and 50.0% negative agreement for HN1:100 and HN1:10 categories, respectively (Table 2).

For Lot-to-Lot Reproducibility, the overall percent agreement was 100% for MP, LP and Neg categories. The Lot-to-Lot Reproducibility results demonstrated 96.7% and 64.4% negative agreement for HN1:100 and HN1:10 categories, respectively (Table 3).

Site-to Site and Lot-to-Lot Reproducibility performance was acceptable for the LP, MP, and Neg sample categories. No specific acceptance criteria were defined for either of the high negative sample categories.

Lot-to-Lot and Site-to-Site quantitative reproducibility study results for positive and negative samples were stratified as follows (see Tables 2 to 5):

- Within run
- Between runs within day
- Between days within lot

- Between lots

Table 2. Lot-to-Lot Quantitative Reproducibility Study Results across Lots, Days and Runs, and within Run for Positive Samples[1]

EP			Within Run		Between Run within Day		Between Day within Lot		Between Lot		Overall	
Category	N	Mean	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
HN1:10	32	316.1	101.89	32.2%	53.21	16.8%	0.00	0.0%	0.00	0.0%	114.95	36.4%
LP	90	748.6	167.05	22.3%	74.75	10.0%	21.14	2.8%	64.47	8.6%	195.18	26.1%
MP	90	975.6	201.66	20.7%	47.85	4.9%	41.24	4.2%	58.00	5.9%	219.14	22.5%

SDPA			Within Run		Between Run within Day		Between Day within Lot		Between Lot		Overall	
Category	N	Mean	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
HN1:10	32	34.4	0.73	2.1%	0.29	0.8%	0.00	0.0%	0.58	1.7%	0.97	2.8%
LP	90	32.8	0.74	2.3%	0.21	0.6%	0.00	0.0%	0.16	0.5%	0.78	2.4%
MP	90	32.1	0.80	2.5%	0.00	0.0%	0.00	0.0%	0.06	0.2%	0.80	2.5%

SDPH			Within Run		Between Run within Day		Between Day within Lot		Between Lot		Overall	
Category	N	Mean	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
HN1:10	32	3.7	1.37	37.3%	0.47	12.7%	0.00	0.0%	0.00	0.0%	1.45	39.4%
LP	90	9.4	2.34	24.8%	0.89	9.5%	0.28	3.0%	0.89	9.4%	2.67	28.3%
MP	90	12.8	2.96	23.1%	0.72	5.6%	0.54	4.2%	1.36	10.6%	3.38	26.3%

[1]Values shown are those obtained for the *C. difficile* target in the samples that gave a positive result

Table 3. Lot-to-Lot Quantitative Reproducibility Study Results across Lots, Days and Runs, and within Run for Negative Samples[1]

EP			Within Run		Between Run within Day		Between Day within Lot		Between Lot		Overall	
Category	N	Mean	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
HN1:100	87	5361.3	510.44	9.5%	219.72	4.1%	0.00	0.0%	455.55	8.5%	718.58	13.4%
HN1:10	58	5296.7	656.51	12.4%	432.84	8.2%	0.00	0.0%	361.57	6.8%	865.50	16.3%
Neg	90	5432.3	543.30	10.0%	148.59	2.7%	0.00	0.0%	498.52	9.2%	752.18	13.8%

SDPA			Within Run		Between Run within Day		Between Day within Lot		Between Lot		Overall	
Category	N	Mean	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
HN1:100	87	29.0	0.40	1.4%	0.00	0.0%	0.09	0.3%	0.40	1.4%	0.57	2.0%
HN1:10	58	29.0	0.29	1.0%	0.00	0.0%	0.05	0.2%	0.50	1.7%	0.58	2.0%
Neg	90	29.0	0.37	1.3%	0.00	0.0%	0.00	0.0%	0.43	1.5%	0.57	2.0%

SDPH			Within Run		Between Run within Day		Between Day within Lot		Between Lot		Overall	
Category	N	Mean	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
HN1:100	87	69.5	6.58	9.5%	1.97	2.8%	0.00	0.0%	4.10	5.9%	8.00	11.5%
HN1:10	58	68.9	7.72	11.2%	5.04	7.3%	0.00	0.0%	2.83	4.1%	9.64	14.0%
Neg	90	69.5	6.56	9.4%	2.09	3.0%	0.00	0.0%	4.52	6.5%	8.23	11.8%

[1]Calculated for the Specimen Processing Control of negative samples

Table 4. Site-to-Site Quantitative Reproducibility Study Results for the Target across Sites, Days and Runs and within Run using one Lot for Positive Samples[1]

EP			Within Run		Between Run within Day		Between Day within Site		Between Site		Overall	
Category	**N**	**Mean**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**
HN1:100	7	279.7	56.11	20.1%	0.00	0.0%	186.31	66.6%	0.00	0.0%	194.58	69.6%
HN1:10	45	314.7	151.79	48.2%	67.47	21.4%	0.00	0.0%	12.53	4.0%	166.58	52.9%
LP	90	948.8	149.65	15.8%	89.99	9.5%	0.00	0.0%	361.55	38.1%	401.51	42.3%
MP	90	1217.4	224.30	18.4%	150.77	12.4%	0.00	0.0%	374.72	30.8%	462.02	37.9%

SDPA			Within Run		Between Run within Day		Between Day within Site		Between Site		Overall	
Category	**N**	**Mean**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**
HN1:100	7	33.4	2.17	6.5%	5.53	16.6%	0.00	0.0%	0.00	0.0%	5.94	17.8%
HN1:10	45	35.1	0.95	2.7%	0.20	0.6%	0.32	0.9%	0.55	1.6%	1.16	3.3%
LP	90	32.5	0.60	1.8%	0.00	0.0%	0.19	0.6%	0.45	1.4%	0.77	2.4%
MP	90	31.6	0.75	2.4%	0.19	0.6%	0.00	0.0%	0.26	0.8%	0.82	2.6%

SDPH			Within Run		Between Run within Day		Between Day within Site		Between Site		Overall	
Category	**N**	**Mean**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**
HN1:100	7	3.9	0.23	5.9%	0.00	0.0%	2.99	76.5%	0.00	0.0%	2.99	76.7%
HN1:10	45	4.2	2.34	55.8%	0.96	23.0%	0.00	0.0%	0.00	0.0%	2.53	60.4%
LP	90	13.1	2.37	18.2%	1.36	10.4%	0.00	0.0%	5.28	40.4%	5.94	45.5%
MP	90	17.6	3.83	21.8%	2.42	13.7%	0.00	0.0%	5.50	31.3%	7.13	40.5%

[1]Values shown are those obtained for the *C. difficile* target in the samples that gave a positive result.

Table 5. Site-to-Site Quantitative Reproducibility Study Results across Sites, Days and Runs and within Run using one Lot for Negative Samples[1]

EP			Within Run		Between Run within Day		Between Day within Site		Between Site		Overall	
Category	N	Mean	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
HN1:100	83	5020.4	631.46	12.6%	162.27	3.2%	0.00	0.0%	417.35	8.3%	774.12	15.4%
HN1:10	45	5006.5	524.23	10.5%	250.03	5.0%	0.00	0.0%	421.67	8.4%	717.73	14.3%
Neg	90	5166.0	554.66	10.7%	204.88	4.0%	0.00	0.0%	543.70	10.5%	803.26	15.5%

SDPA			Within Run		Between Run within Day		Between Day within Site		Between Site		Overall	
Category	N	Mean	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
HN1:100	83	28.8	0.35	1.2%	0.00	0.0%	0.00	0.0%	0.18	0.6%	0.39	1.4%
HN1:10	45	28.8	0.32	1.1%	0.00	0.0%	0.00	0.0%	0.16	0.5%	0.35	1.2%
Neg	90	28.7	0.27	0.9%	0.00	0.0%	0.00	0.0%	0.14	0.5%	0.30	1.1%

SDPH			Within Run		Between Run within Day		Between Day within Site		Between Site		Overall	
Category	N	Mean	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
HN1:100	83	64.8	9.84	15.2%	0.00	0.0%	0.00	0.0%	4.65	7.2%	10.89	16.8%
HN1:10	45	64.5	7.47	11.6%	2.15	3.3%	0.00	0.0%	4.43	6.9%	8.94	13.9%
Neg	90	67.0	6.51	9.7%	2.40	3.6%	0.00	0.0%	6.55	9.8%	9.54	14.2%

[1]Calculated for the Specimen Processing Control of negative samples

Second Derivative Peak Abscissa (SDPA), an internal criteria used to determine a final assay result, was selected as an additional means of assessing assay reproducibility. Overall mean SDPA values with variance components (SD and %CV) are shown in Tables 6 and 7.

Table 6: Site-To-Site Reproducibility Study Results using One Lot of the BD MAX™ Cdiff Assay

Category	SITE						Overall Percent Agreement		SDPA Values[1]		
	Site 1 Percent Agreement		Site 2 Percent Agreement		Site 3 Percent Agreement				Overall Mean	SD	%CV
Neg[1]	30/30	100.0%	30/30	100.0%	30/30	100.0%	100.0%	(95% CI: 95.9%, 100.0%)	28.7	0.30	1.1
HN1:100[1,2]	28/30	93.3%	25/30	83.3%	30/30	100.0%	92.2%	(95% CI: 84.8%, 96.2%)	28.8	0.39	1.4
HN1:10[1,2]	17/30	56.7%	8/30	26.7%	20/30	66.7%	50.0%	(95% CI: 39.9%, 60.1%)	28.8	0.35	1.2
LP	30/30	100.0%	30/30	100.0%	30/30	100.0%	100.0%	(95% CI: 95.9%, 100.0%)	32.5	0.77	2.4
MP	30/30	100.0%	30/30	100.0%	30/30	100.0%	100.0%	(95% CI: 95.9%, 100.0%)	31.6	0.82	2.6

[1]For the Negative and High Negative categories, SDPA values reported are for the SPC. For other categories, SDPA values reported are for the toxigenic *C. difficile* target.
[2] For the High Negative categories, the expected assay result was deemed to be negative. Therefore, percent agreement was calculated for negative results.

Table 7: Lot-to-Lot Reproducibility Study Results using Three Lots of the BD MAX™ Cdiff Assay

Category	LOT						Overall Percent Agreement		SDPA Values[1]		
	Lot 1 Percent Agreement		Lot 2 Percent Agreement		Lot 3 Percent Agreement				Overall Mean	SD	%CV
Neg[1]	30/30	100.0%	30/30	100.0%	30/30	100.0%	100.0%	(95% CI: 95.9%, 100.0%)	29.0	0.57	2.0
HN1:100[1,2]	29/30	96.7%	28/30	93.3%	30/30	100.0%	96.7%	(95% CI: 90.7%, 98.9%)	29.0	0.57	2.0
HN1:10[1,2]	17/30	56.7%	21/30	70.0%	20/30	66.7%	64.4%	(95% CI: 54.2%, 73.6%)	29.0	0.58	2.0
LP	30/30	100.0%	30/30	100.0%	30/30	100.0%	100.0%	(95% CI: 95.9%, 100.0%)	32.8	0.78	2.4
MP	30/30	100.0%	30/30	100.0%	30/30	100.0%	100.0%	(95% CI: 95.9%, 100.0%)	32.1	0.80	2.5

[1]For the Negative and High Negative categories, SDPA values reported are for the SPC. For other categories, SDPA values reported are for the toxigenic *C. difficile* target.
[2] For the High Negative categories, the expected assay result was deemed to be negative. Therefore, percent agreement was calculated for negative results.

Sample Storage

Collected specimens can be stored at 2-25°C for a maximum of 48 hours or at 2-8°C for a maximum of 120 hours (5 days) before testing. In case of repeat testing from the Sample Buffer Tube, the following storage conditions apply:

- up to 5h after the end of the initial run when stored at 25 ± 2°C or
- up to 120h after the end of the initial run when stored at 2-8°C.

Controls

External Control materials are not provided by BD. Various types of External Controls are recommended to allow the user to select the most appropriate for their laboratory quality control program:

- Commercially available control materials (e.g., ATCC® 43255, a *C. difficile* strain bearing the *tcdB* gene, and ATCC® 700057, a non-toxigenic *C. difficile* strain, can be used as positive and negative controls, respectively);
- Suspensions of bacterial strains characterized by the user as toxigenic or non-toxigenic;

- Previously characterized clinical specimens known to be positive or negative for toxigenic *C. difficile*.

The assay includes a Sample Processing Control (SPC) that is present in the Extraction Tube. The SPC monitors DNA extraction steps, thermal cycling steps, reagent integrity and the presence of inhibitory substances.

Analytical Sensitivity
The analytical sensitivity (Limit of Detection or LoD) for the BD MAX™ Cdiff Assay was determined as follows: individual inoculating loops were dipped into *C. difficile* bacterial suspensions at different concentrations, prepared and quantified from cultures of four *C. difficile* strains representing three toxinotypes (0, III, VIII). Nine bacterial concentrations ranging between 0 and 64,000 CFU/mL were tested for each toxinotype. Each loop was then transferred to a SBT, already containing fecal matrix negative for toxigenic *C. difficile*. Each *C. difficile* strain was tested in replicates of 24 per concentration, by two different operators, using three different production lots of the BD MAX™ Cdiff Assay. The results were analyzed using a statistical linear logistic model. Briefly, the method models the positive response (expressed in percentage) as a function of Log (CFU/mL). The logistic model equation for the fitted curve allows the computation of the LoD by inverse prediction using the parameter estimates and their 95% confidence interval. The LoD was defined as the lowest concentration at which 95% of all replicates tested positive. The LoD ranged from 125 to 265 CFU per loop for each strain (Table 8).

Table 8: Limit of Detection of the BD MAX™ Cdiff Assay

***C. difficile* Strain**	**Toxinotype**	**LoD in CFU per loop**
ATCC® 43255	0	265 (95% CI: 140, 502)
ATCC® 9689	0	156 (95% CI: 82, 298)
ATCC® BAA-1805	III	205 (95% CI: 102, 412)
ATCC® 43598	VIII	125 (95% CI: 66, 235)

Analytical Inclusivity
A variety of toxigenic *C. difficile* strains were included in this study taking into account geographic origin, toxinotype, NAP1 outbreaks and temporal diversity. Sixty-four (64) strains including 23 toxinotypes and representing 21 countries were tested, including strains from public collections and well-characterized clinical isolates (see Table 9). The assay correctly identified 62 of the 64 toxigenic *C. difficile* strains which were tested at ~3xLoD. Two (2) strains produced low signal results and were false-negative in one out of five replicates.

Table 9: Strains Tested in the Inclusivity Study of the BD MAX™ Cdiff Assay.

Strain ID	Toxinotype	Strain ID	Toxinotype	Strain ID	Toxinotype
ATCC 700792 (14797-2)	ND[1]	DII1	ND[1]	M30761	VI
ATCC 17858 (1253)		QI1		57267	VII
ATCC 51695 (BDMS 18AN)		MI23		ATCC 43598	VIII
ATCC 43600 (2149)		EII1		51680	IX
ATCC 43599 (2022)		PI2		M46722	IX
ATCC 43596 (545)		M14614	0	M40767	IX
ATCC 43594 (W1194)		M39177	0	8864	X
ATCC 17857 (870)		ATCC 43255	0	M26479	XII
ATCC BAA-1382 (630)		ATCC 9689	0	IS25	XII[2]
141		M16256	I	R9367	XIII
CD11		AC008	II	R10870	XIV
301		M14473	III	R9385	XV[2]
CD 246		M28681	III	SUC36	XVI
NCTC 11382		M37992	III	J9965	XVII
NCTC 11204		M41124	III	K095	XVIII
NI1		M1137	III	TR13	XIX
CI3		ATCC BAA-1805	III	CH6223	XXI
FI9		SE844	IIIa	M13883	XXI
LI6		55767	IV	8785	XXIII
KI3		M25097	IV	597B	XXIV
GII1		SE881	V		
HI1		51377	VI		

[1] ND = Not Determined.

[2] The repeat result is presented here. The initial result was negative. Positive results were obtained upon retest from SBT and in an additional test performed with 3 replicates. Overall, 4/5 test results were found positive.

Analytical Specificity

The BD MAX™ Cdiff Assay was performed on samples containing phylogenetically related species *(Clostridium* other than toxigenic *C. difficile*) and other organisms (bacteria, viruses) likely to be found in stool specimens (Table 10).

- Six (6) out of six *C. difficile* strains not bearing the *tcdB* gene, tested at a concentration ≥ 1 X 10^8 CFU/mL, produced negative results with the BD MAX™ Cdiff Assay;
- Thirty (30) out of 30 *Clostridium* strains other than *C. difficile*, including four strains of *C. sordellii*, tested at a concentration ≥ 1 X 10^8 CFU/mL, produced negative results with the BD MAX™ Cdiff Assay;
- Ninety-five (95) out of 98 other bacterial strains, including 93 species and subspecies, were tested at a concentration ≥ 1 X 10^8 CFU/mL (or ~ 1 X 10^8 genomic DNA cp/mL or 1 X 10^8 elementary bodies/mL) and produced negative results with the BD MAX™ Cdiff Assay. The following strains gave a positive result:
  - *Bacteroides stercoris* (ATCC 43183)
  - *Gemella morbillorum* (ATCC 27824)

- *Peptoniphilus asaccharolyticus* (ATCC 14963)

An investigation was conducted and determined that the false-positive results were due to contamination. Overall, out of 5 replicates, the three strains each gave an initial positive result due to contamination. ATCC 27824 gave negative results for the 4 other replicates. However, ATCC 43183 and ATCC 27824 gave another positive result due to instrument issue and the 3 last replicates were found negative.

- Seven (7) out of seven viruses, tested at a concentration ≥ 1 X 10^5 PFU/mL, produced negative results with the BD MAX™ Cdiff Assay.

Table 10: Species Tested for the Cross-Reactivity Study

***Clostridium* species (≥ 1x10⁸ CFU/mL)**		
Clostridium beijerinckii	*Clostridium histolyticum*	*Clostridium septicum*
Clostridium bifermentans	*Clostridium innocuum*	*Clostridium sordellii*
Clostridium bolteae	*Clostridium nexile*	*Clostridium lavalense*
Clostridium butyricum	*Clostridium novyi*	*Clostridium sphenoides*
Clostridium chauvoei	*Clostridium orbiscindens*	*Clostridium spiroforme*
Clostridium difficile (non-toxigenic strains)	*Clostridium paraputrificum*	*Clostridium sporogenes*
Clostridium difficile (XIa (A-B-tox bin+) and XIb)	*Clostridium perfringens*	*Clostridium symbiosum*
Clostridium fallax	*Clostridium ramosum*	*Clostridium tertium*
Clostridium haemolyticum	*Clostridium scindens*	*Clostridium tetani*
Other Bacterial Species (≥ 1x10⁸ CFU/mL)		
Abiotrophia defectiva	*Enterococcus faecium VanA*	*Plesiomonas shigelloides*
Acinetobacter baumannii	*Enterococcus gallinarum*	*Porphyromonas asaccharolytica*
Acinetobacter lwoffii	*Enterococcus hirae*	*Prevotella melaninogenica*
Aeromonas hydrophila	*Enterococcus raffinosus*	*Proteus mirabilis*
Alcaligenes faecalis subsp. faecalis	*Escherichia coli*	*Proteus penneri*
Anaerococcus tetradius	*Escherichia fergusonii*	*Providencia alcalifaciens*
Bacillus cereus	*Escherichia hermannii*	*Providencia rettgeri*
Bacteroides caccae	*Fusobacterium varium*	*Providencia stuartii*
Bacteroides stercoris	*Gardnerella vaginalis*	*Pseudomonas aeruginosa*
Bifidobacterium adolescentis	*Gemella morbillorum*	*Pseudomonas putida*
Bifidobacterium longum	*Hafnia alvei*	*Ruminococcus bromii*
Campylobacter coli	*Helicobacter cinaedi*	*Salmonella enterica subsp. enterica*
Campylobacter jejuni subsp. jejuni	*Helicobacter pylori*	*Salmonella enterica subsp. arizonae*
Candida albicans	*Klebsiella oxytoca*	*Serratia liquefaciens*
Candida catenulata	*Klebsiella oxytoca*	*Serratia marcescens*
Cedecea davisae	*Klebsiella pneumoniae subsp. pneumoniae*	*Shigella boydii*
Citrobacter amalonaticus	*Lactobacillus acidophilus*	*Shigella dysenteriae*
Citrobacter freundii	*Lactobacillus reuteri*	*Shigella sonnei*
Citrobacter koseri	*Lactococcus lactis subsp. lactis*	*Staphylococcus aureus subsp. aureus*
Citrobacter sedlakii	*Leminorella grimontii*	*Staphylococcus epidermidis*
Collinsella aerofaciens	*Listeria grayi*	*Stenotrophomonas maltophilia*

Corynebacterium genitalium	*Listeria innocua*	*Streptococcus agalactiae*
Desulfovibrio piger	*Listeria monocytogenes*	*Streptococcus dysgalactiae subsp. dysgalactiae*
Edwardsiella tarda	*Mitsuokella multacida*	*Streptococcus intermedius*
Eggerthella lenta	*Mobiluncus curtisii subsp. holmesii*	*Streptococcus uberis*
Enterobacter aerogenes	*Moellerella wisconsensis*	*Trabulsiella guamensis*
Enterobacter cloacae subsp. cloacae	*Morganella morganii subsp. morganii*	*Veillonella parvula*
Enterococcus casseliflavus	*Neisseria gonorrhoeae*	*Vibrio parahaemolyticus*
Enterococcus cecorum	*Parabacteroides merdae*	*Yersinia bercovieri*
Enterococcus dispar	*Peptoniphilus asaccharolyticus*	*Yersinia rohdei*
Enterococcus faecalis	*Peptostreptococcus anaerobius*	
Intracellular bacteria ($1x10^8$ elementary bodies/mL)	***Vibrio cholerae* species ($\sim 1x10^8$ cp/mL)**	***Human sample ($\sim 1x10^8$ cp/mL)***
Chlamydia trachomatis	*Vibrio cholerae*	*Homo sapiens*
virus ($\geq 1x10^5$ PFU/mL)		
Adenovirus Type 14	Enterovirus	Cytomegalovirus, Strain AD-169
Rotavirus, stain WA	Echovirus 19 (Strain Burke)	
Norovirus group 1	Coxsackie virus B1 (Com-5)	

Interfering Substances

Twenty-five (25) biological and chemical substances occasionally used or found in perianal, rectal and/or stool specimens were evaluated for potential interference with the BD MAX™ Cdiff Assay. Two (2) organisms (*E. coli* ATCC 25922 and non-toxigenic *C. difficile* ATCC 700057) were also tested at high loads in order to assess bacterial interference. Toxigenic *C. difficile* negative specimens and toxigenic *C. difficile* positive specimens at 2-3X LoD were tested with the highest amount of each compound likely to be found in the specimens or with interfering organisms (1 X 10^8 CFU/mL of each strain). Potentially interfering substances include calcium carbonate (Tums®) as well as magnesium and aluminum hydroxide (Maalox® liquid). Results demonstrated no reportable interference with any other tested substance except for Mesalamine rectal suspension enema and Gynol II® that both showed slight inhibition (delay of Second Derivative Peak Abscissa) in the BD MAX™ Cdiff Assay, however, expected assay results were still obtained (Table 11).

Table 11: Endogenous and Commercial Exogenous Substances tested with the BD MAX™ Cdiff Assay

Brand Name or Description	Weight or Volume Tested/SBT	Result	Brand Name or Description	Weight or Volume Tested/SBT	Result
Nystatin	10 µL	NI	Pepto Bismol™	10 µL	NI
Hyderm™ Hydrocortisone (cream)	0.0246 g	NI	Ex-Lax®	0.0134 g	NI
Glycerin Suppositories	0.0129 g	NI	Metronidazole	10 µL	NI
Ihle's Paste	0.0388 g	NI	Vancomycin	10 µL	NI
Anusol® Plus	0.0123 g	NI	Polysporin®	0.0240 g	NI
Preparation H® with Bio-Dyne® (cream)	0.0222 g	NI	Naproxen	10 µL	NI
Major Prep® with Phenylephrine	0.0111 g	NI	Tucks® Personal Cleansing Pads	3 mm^2	NI
Tums®	0.0395 g	I	Triglyceride Mix (C2-C10)	10 µL	NI
Maalox® (liquid)	10 µL	I	Palmitic Acid	25 mg	NI
Mesalamine Rectal Suspension Enema	10 µL	*	Stearic Acid	10 mg	NI
Fleet® Mineral Oil Enema	0.0182 g	NI	Blood	10 µL	NI
Gynol II® Vaginal Contraceptive (with Nonoxynol-9)	0.0262 g	*	Mucus	10 µL	NI
Imodium AD®	0.0062 g	NI	*E. coli* + non-toxigenic *C. difficile*	10 µL	NI

I: Interference with the BD MAX™ Cdiff Assay.
NI: No reportable interference with the BD Cdiff™ Assay.
* Mesalamine rectal suspension enema and Gynol II® (with nonoxynol-9) showed slight inhibition (delay of Second Derivative Peak Abscissa) in the BD MAX™ Cdiff Assay, however, expected assay results were still obtained.

Carryover / Cross-Contamination

A study was conducted to investigate within-run carryover and between-run carryover while processing specimens with high bacterial load of toxigenic *C. difficile* in the BD MAX™ Cdiff assay. A panel made of one high positive member and one negative member was used to prepare numerous samples. A *Clostridium difficile* strain (Tox 0, ATCC 9689) was used for the high positive *C. difficile* panel member (~$3x10^8$ CFU/mL). The negative member did not contain any target analyte. Twelve (12) replicates of the high positive panel member and 12 replicates of the negative panel member were tested in each run by alternating negative and positive samples. Three (3) operators performed 3 consecutive runs for a total of 9 runs of 24 samples. There were no false positive results due to carry-over contamination.

Clinical Performance Studies

Clinical performance characteristics of the BD MAX™ Cdiff Assay were determined in a multi-site prospective investigational study. Six (6) investigational centers participated in the study. To be enrolled in the study, specimens had to be from patients suspected of having *C. difficile* infection for which diagnostic tests were indicated and ordered. Only soft or liquid stools, and only one specimen per patient, were included.

The Comparative Reference Method consisted of direct culture complemented by enriched culture. Enriched culture analysis was completed for all specimens that were negative for

toxigenic *C. difficile* by direct culture. The anaerobic culture was used to isolate *C. difficile*, if present. This was followed by confirmation of the isolate identification and a Tissue Culture Cytotoxicity Assay to determine the toxigenicity of the isolate.

Of the 2071 soft or liquid stool specimens compliant with the Reference Method (Direct and Enriched Culture), 1819 gave compliant and reportable results with the BD MAX ™Cdiff Assay. In comparison to the Reference Method, the BD MAX™ Cdiff Assay identified 87.7% of the toxigenic *C. difficile* positive specimens and 96.8% of the toxigenic C. difficile negative specimens (Tables 12 and 13).

Table 12: Results Obtained with the BD MAX™ Cdiff Assay in Comparison to the Reference Method

All Sites		**Reference Method**		
		+	**-**	**Total**
BD MAX™ Cdiff Assay	**+**	**265**	**48**[1]	**313**
	-	**37**[1]	**1469**	**1506**
	Total	**302**	**1517**	**1819**
Sensitivity: 87.7% (265/302) (95% CI: 83.6%, 91.0%) **Specificity: 96.8% (1469/1517) (95% CI: 95.8%, 97.6%)** **PPV: 83.5% (95% CI: 79.4%, 87.1%)** **NPV: 97.7% (95% CI: 97.0%, 98.4%)**				

[1] Further investigation was performed on specimens with discordant results between the Reference Method and the BD MAX™ Cdiff Assay.

- 27 of 48 False Positive BD MAX™ Cdiff specimens were also found to be positive using another commercially available FDA-cleared RT-PCR assay targeting the *C. difficile tcdB* gene.
- 32 of 37 False Negative BD MAX™ Cdiff specimens, were also found to be negative using another commercially available FDA-cleared RT-PCR assay targeting the *C. difficile tcdB* gene.

Table 13. Results Obtained by Site using the BD MAX™ Cdiff Assay in Comparison to the Reference Method

Site	**Sensitivity**	**Specificity**
Site 1	90.0% (18/20) (69.9%, 97.2%)[1]	95.3% (202/212) (91.5%, 97.4%)
Site 2	84.4% (38/45) (71.2%, 92.3%)	95.3% (205/215) (91.7%, 97.5%)
Site 3	94.7% (36/38) (82.7%, 98.5%)	97.9% (275/281) (95.4%, 99%)
Site 4	83.8% (31/37) (68.9%, 92.3%)	95.8% (322/336) (93.1%, 97.5%)
Site 5	96.1% (49/51) (86.8%, 98.9%)	98.4% (186/189) (95.4%, 99.5%)
Site 6	83.8% (93/111) (75.8%, 89.5%)	98.2% (279/284) (95.9%, 99.2%)
Overall Study	**87.7% (265/302)** **(83.6%, 91.0%)**	**96.8% (1469/1517)** **(95.8%, 97.6%)**

[1]Numbers in parentheses express the 95% confidence interval boundaries

In comparison to direct culture, the BD MAX™ Cdiff Assay identified 96.5% of the toxigenic *C. difficile* positive specimens and 92.7% of the toxigenic *C. difficile* negative specimens (Tables 14 and 15).

Table 14: Results Obtained with the BD MAX™ Cdiff Assay in Comparison to Direct Culture

All Sites		**Direct Culture**		
		+	**-**	**Total**
BD MAX™ Cdiff Assay	**+**	**194**	**118**	**312**
	-	**7**	**1507**	**1514**
	Total	**201**	**1625**	**1826**
Positive Percent Agreement: 96.5% (194/201) (95% CI: 93.0%, 98.3%) **Negative Percent Agreement: 92.7% (1507/1625) (95% CI: 91.4%, 93.9%)**				

Table 15. Results Obtained by Site using the BD MAX™ Cdiff Assay in Comparison to Direct Culture

Site	**SensitivityPositive Percent Agreement**	**Negative Percent Agreement**
Site 1	92.9% (13/14) (68.5%, 98.7%)[1]	93.1% (203/218) (89.0%, 95.8%)
Site 2	100.0% (26/26) (87.1%, 100%)	90.6% (213/235) (86.2%, 93.7%)
Site 3	96.0% (24/25) (80.5%, 99.3%)	93.9% (276/294) (90.5%, 96.1%)
Site 4	93.8% (15/16) (71.7%, 98.9%)	91.7% (330/360) (88.4%, 94.1%)
Site 5	95.7% (45/47) (85.8%, 98.8%)	96.4% (188/195) (92.8%, 98.3%)
Site 6	97.3% (71/73) (90.5%, 99.2%)	92.0% (297/323) (88.5%, 94.4%)
Overall Study	**96.5% (194/201)** **(93.0%, 98.3%)**	**92.7% (1507/1625)** **(91.4%, 93.9%)**

[1]Numbers in parentheses express the 95% confidence interval boundaries

Out of 1860 soft or liquid stool specimens tested with the BD MAX™ Cdiff Assay, 58 (3.1%) were initially reported as unresolved. 42 of those were repeated and 32 were resolved upon repeat testing. Overall, 0.5% remained unresolved after repeat (Table 16).

Table 16: Unresolved Rate

Initial Unresolved Rate	**Unresolved Rate After Repeat**
3.1% (58/1860)* (95% CI: 2.4%, 4.0%)	**0.5% (10/1844) (95% CI: 0.3%, 1.0%)**

* Total number based on compliant specimens and BD MAX™ Cdiff Assay results.

Out of 1916 soft or liquid stool specimens tested with the BD MAX™ Cdiff Assay, 21 (1.1%) were initially reported as indeterminate. Out of a total of 1844 compliant results, no result remained Indeterminate upon repeat (considering valid results and compliant repeats).

Out of 1916 soft or liquid stool specimens tested with the BD MAX™ Cdiff Assay, 28 (1.5%) were initially reported as incomplete. Out of a total of 1844 compliant results, no result remained Incomplete upon valid repeat (considering valid results and compliant repeats).

Comparison Studies

In addition to the multi-site investigational study, a comparison study was performed using the BD MAX™ Cdiff assay and two (2) commercially available FDA-cleared molecular assays for the detection of the *C. difficile tcdB* gene. Testing was performed on 2013 specimens at two external sites.

In comparison to one FDA-cleared molecular test (Table 10a), the PPA and NPA of the BD MAX™ Cdiff Assay were 99.1% (CI: 94.9%-99.8%) and 97.4% (CI: 95.7%-98.4%), respectively.

In comparison to a second FDA-cleared molecular test (Table 10b), the PPA and NPA of the BD MAX™ Cdiff Assay were 95.5% (CI: 92.1%-97.5%) and 98.8% (CI: 97.9%-99.3%), respectively.

Table 17a: Results Obtained with the BD MAX™ Cdiff Assay in Comparison to a Commercially Available FDA-cleared Molecular Assay for *C. difficile*.

All Sites		**FDA-cleared Molecular Assay 1**		
		+	**-**	**Total**
BD MAX™ Cdiff Assay	**+**	**106**	**14**	**120**
	-	**1**	**526**	**527**
	Total	**107**	**540**	**647**
Positive Percent Agreement: 99.1% (95% CI: 94.9%, 99.8%) **Negative Percent Agreement: 97.4% (95% CI: 95.7%, 98.4%)**				

Table 17b: Results Obtained with the BD MAX™ Cdiff Assay in Comparison to a second Commercially Available FDA-cleared Molecular Assay for *C. difficile*.

All Sites		FDA-cleared Molecular Assay 2		
		+	-	Total
BD MAX™ Cdiff Assay	+	233	14	247
	-	11	1108	1119
	Total	244	1122	1366
Positive Percent Agreement: 95.5% (95% CI: 92.1%, 97.5%) **Negative Percent Agreement: 98.8% (95% CI: 97.9%, 99.3%)**				

Expected Values

In the BD MAX™ Cdiff Assay clinical study a total of 1834 reportable results, from specimens compliant at the specimen and PCR levels, were obtained from 6 geographically diverse sites and compared with Direct and Enriched culture. The study population was grouped into in-patient, out-patient and unknown categories. The number and percentage of positive cases, as determined by the BD MAX™ Cdiff Assay, are presented in Table 18 below.

Table 18: Expected Values

		BD MAX™ Cdiff Assay		
Group	Total Number of Specimens[1]	Number Positive	Number Negative	Positive Percentage
In-patient	1249	184	1065	14.7% (184/1249)
Out-patient	457	114	343	24.9% (114/457)
Unknown	128	17	111	13.3% (17/128)
Total[1]	1834	315	1519	17.2% (315/1834)

[1]Total number of specimens based on compliant PCR results

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Center – WO66-G609
Silver Spring, MD 20993-0002

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GENEOHM SCIENCES CANADA, INC. (BD DIAGNOSTICS)
2555 BOUL. DU PARC-TECHNOLOGIQUE
QUEBEC (QUEBEC) G1P 4S5
CANADA

April 2, 2013

Re: K130470
Trade/Device Name: Bd MAX Cdiff Assay
Regulation Number: 21 CFR 866.3130
Regulation Name: *Clostridium difficile* Toxin Gene Amplification Assay
Regulatory Class: II
Product Code: OZN, OOI
Dated: February 22, 2013
Received: February 27, 2013

Dear Dr. Dionne:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Parts 801 and 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

If you desire specific advice for your device on our labeling regulations (21 CFR Parts 801 and 809), please contact the Office of *In Vitro* Diagnostics and Radiological Health at (301) 796-5450. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm.

Sincerely yours,

Uwe Scherf -S for

Sally A. Hojvat, M.Sc., Ph.D.
Director
Division of Microbiology Devices
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health

Enclosure

1.2 Indications for Use Statement

510(k) Number (if known): K130470

Device Name: BD MAX™ Cdiff Assay

Intended Use:

The BD MAX™ Cdiff Assay performed on the BD MAX™ System is an automated *in vitro* diagnostic test for the direct, qualitative detection of the *Clostridium difficile* toxin B gene (*tcdB*) in human liquid or soft stool specimens from patients suspected of having *C. difficile* infection (CDI). The test, performed directly on the specimen, utilizes real-time polymerase chain reaction (PCR) for the amplification of *C. difficile* toxin B gene DNA and fluorogenic target-specific hybridization probes for the detection of the amplified DNA. The BD MAX™ Cdiff Assay is intended to aid in the diagnosis of CDI.

Prescription Use XXX
(Per 21 CFR 801.109)

OR

Over-The-Counter Use
(Optional Format 1-2-96)

(PLEASE DO NOT WRITE BELOW THIS LINE - CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of In Vitro Diagnostic Devices Evaluation and Safety (OIVD)

Raquel A. Peat -S
2013.04.02 12:52:34 -04'00'

Division Sign-Off
Office of In Vitro Diagnostics and Radiological Health
510(k) K130470